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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

RAO, M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/246,451	Applicant(s) Arnold et al.
	Examiner Manjunath N. Rao	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on Apr 4, 2001
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 1035 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-145 is/are pending in the application.
- 4a) Of the above, claim(s) 1-106, 126-129, 132, and 137-145 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 7-125, 130-131, 133-136 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7, 10
- 18) Interview Summary (PTO-413) Paper No(s). _____
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other: _____

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DETAILED ACTION

1. Claims 1-145 are still at issue and are present for examination.

Election/Restriction

2. Applicant's election with traverse of Group VI, Claims 107-125, 130-131, 133-136 and species election in Paper No. 9 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I-V and VII-IX would not be undue burden on the Examiner. This is not found persuasive because while the searches for groups I-V and VII-IX may overlap, they are not coextensive. The search for Groups I -III, VIII and IX, IV-V, VII and III would each require the search of subclasses unnecessary for the search of elected Group VI. For example, search of Group VII would require search of subclass 435/440 and search of Groups IV-V would require search of subclass 435/6. In addition to the above class/subclass searches each of the above group would require extensive non-patent literature search which indeed causes an undue burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-106, 126-129, 132, 137-145 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

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Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Oath/Declaration

4. The oath or declaration is defective. The oath is considered defective because it does not state the US provisional application numbers based upon which the priority dates have been claimed. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

Drawings

5. This application has been filed with drawings that have been objected to by the Draftsperson. Please see the attached form PTO948 for details.

Claim Objections

6. Claims 107-114 and 130-131 are objected to because of the following informalities: Claims 107-114 and 130-131 depend from claims which belong to non elected groups. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 115-121, 130-131, 133-136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 115-121, 130-131, 133-136 are rejected because it recites a short form “P450 oxygenase” for an enzyme without reciting its expansion at the first occurrence. It is also not clear to the Examiner as to what P450 is meant by the applicants. Examiner is aware that, in the art, Cytochrome P450 is sometimes referred to as P450 in short form. However, it is not clear to the Examiner whether applicants mean the same in the claims.

9. Claim 122 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 122 is rejected because it recites a short form “P40 oxygenase” for an enzyme without reciting its expansion at the first occurrence. It is also not clear to the Examiner as to what applicants mean by “P40 oxygenase”.

10. Claim 122 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 122 is rejected because it recites wild-type P450 enzyme with three

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different amino acids at the same position, 331. It is not clear to the Examiner as to how an enzyme can be called a “wild type” if it already differs by three amino acids at the same position. Examiner realizes that applicants intended to recite 3 different positions. Amending the claim accordingly will overcome this rejection.

11. Claim 125 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 125 is rejected because it recites the phrase “a first polynucleotide which hybridizes to a second polypeptide”. It is not clear to the Examiner first, as to what applicants mean by “ a first polynucleotide”, second, it is also not clear as how a polynucleotide can hybridize to a polypeptide.

12. Claim 130 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 130 is rejected because it recites a phrase “ with a provided P450 enzyme”. It is not clear to the Examiner as to what applicants mean by “provided enzyme”.

13. Claim 115-125, 130, 131, 133-136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 115-125, 130, 131, 133-136 are rejected because all the above claims are drawn to a variant enzyme whose characteristics are compared to a wild-type enzyme. However, it is not clear to the Examiner as to which specific cytochrome P450 oxygenase is considered as “wild-type” by the applicant. Cytochrome P450 oxygenases are a superfamily of proteins found in microorganisms, animals and plants. It is also well known that there is amino acid sequence variations among the “wild-types” of microorganisms, plants and animals. Furthermore, unless applicants specify a particular SEQ ID NO for their wild-type whose amino acid positions correspond to the amino acid positions of the variant claimed in the above claims, it will be impossible for the Examiner to do a proper search of the variant amino acid sequences..

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 107-125, 130-131 and 133-136 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mutant cytochrome P450 oxygenase isolated from *Ps.putida* in which a glutamic acid at position 331 is changed to lysine, an arginine at position 280 is changed to lysine and a cysteine at position 242 is changed to phenylalanine, does not reasonably provide enablement for any or all other mutant/variant cytochrome P450 oxygenase enzyme from any source. The specification does not enable any person skilled in the art to which

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it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 107-125, 130-131 and 133-136 are so broad as to encompass any protein variant or mutant enzyme from any source or any recombinant cytochrome P450 oxygenase enzyme from any source. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number cytochrome P450 oxygenase enzymes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and to obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the variant enzyme of the genus *Ps.putida* as described above.

While enzyme isolation techniques and recombinant techniques are known, it is not routine in the art to screen multiple sources, multiple substitutions, or multiple modifications, as encompassed by the instant claims, and the reasonable expectation of success in obtaining the desired enzyme are limited due to the complexity of the huge number of microorganisms, animals and plants that need to be analyzed and the result of such isolation from an extremely large number of sources is unpredictable.

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The specification does not support the broad scope of the claims which encompass all or any variant cytochrome P450 oxygenase enzyme of any microorganism, animal or plant because the specification does not establish:(A) a rational and predictable scheme for isolation and characterization of any variant cytochrome P450 oxygenase from any given source with an expectation of obtaining the desired biological activity and function; (B) the general tolerance of cytochrome P450 oxygenase enzymes to modification and extent of such tolerance; and (C) the specification provides insufficient guidance as to which of the infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any variant cytochrome P450 oxygenase enzyme of any microorganism or animal or plant. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

15. Claims 107-125, 130-131 and 133-136 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 107-125, 130-131 and 133-136 are directed to polypeptides corresponding to variants of Cytochrome P450 oxygenase. Claims 107-125, 130-131 and 133-136 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue that have not been disclosed in the specification. No description has been provided of all the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of a single variant with specific amino acid changes at positions 331, 242 and 280 corresponding to a wild-type cytochrome P450 oxygenase amino acid sequence, has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from wild-type cytochrome P450 oxygenase, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions. Therefore many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed

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genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 107-114, 123-125, 130-131, 133-136 are rejected under 35 U.S.C. 102(a) as being anticipated by Manchester(a)et al. Protein Engineering, 1995, Vol 8(8):801-807 or Manchester(b) et al. (Biochemie, 1996, Vol. 78(8-9), 714-722). This rejection is based upon the public availability of printed publications. Claims 107-114, 123-125, 130-131, 133-136, of the instant application are drawn to variant cytochrome P450 oxygenase enzyme which can be identified by a method comprising the steps of providing an organic substrate and an oxygen donor, supplying a test enzyme and a coupling enzyme to promote the formation of a detectable composition, a sequence conservative and a function conservative variant of the above enzyme, wherein the polynucleotide encoding such an enzyme hybridizes to a polynucleotide encoding a

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variant with changes in the amino acid at position 331, a variant having improved enzyme activity and stability to the extent of at least twice or ten times compared to a wild type cytochrome P450. Manchester (a) et al. and Manchester (b) et al. disclose such a variant cytochrome P450 enzyme. Since there is no limitation placed on the position of amino acid and the number of changes that can be present in the amino acid sequence for a variant cytochrome P450 oxygenase, above claims read on the variant enzymes disclosed by Manchester(a) or Manchester(b) et al.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 6:30 a.m. to 3:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-

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3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao
June 1, 2001

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